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Structural brain changes in medically refractory focal epilepsy resemble premature brain aging

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ABSTRACT

Objective: We used whole brain T1-weighted MRI to estimate the age of individuals with medically refractory focal epilepsy, and compared with individuals with newly diagnosed focal epilepsy and healthy controls. The difference between neuroanatomical age and chronological age was compared between the three groups.
Methods: Neuroanatomical age was estimated using a machine learning-based method that was trained using structural MRI scans from a large independent healthy control sample ($N = 2001$). The prediction model was then used to estimate age from MRI scans obtained from newly diagnosed focal epilepsy patients ($N = 42$), medically refractory focal epilepsy patients ($N = 94$) and healthy controls ($N = 74$).
Results: Individuals with medically refractory epilepsy had a difference between predicted brain age and chronological age that was on average 4.5 years older than healthy controls ($p = 4.6 \times 10^{-5}$). No significant differences were observed in newly diagnosed focal epilepsy. Earlier age of onset was associated with an increased brain age difference in the medically refractory group ($p = 0.034$).
Significance: Medically refractory focal epilepsy is associated with structural brain changes that resemble premature brain aging.

1. Introduction

Medically refractory focal epilepsy is associated with decreased brain-wide volumetric measures and cognitive function, both of which are also observed in normal aging (Dabbs et al., 2012; Hoppe et al., 2007; Sowell et al., 2003; Salthouse, 2004). Prior studies have noted that epilepsy-related neuroanatomical and cognitive changes are greater than those observed in normal aging and therefore may be conceptualized as accelerated aging (Breuer et al., 2016; Lin et al., 2012; Bernhardt et al., 2009; Helmstaedter et al., 2003).

Evidence for an association between chronic focal epilepsy and brain atrophy has primarily come from analyses of cortical thickness changes or local gray matter volume in temporal lobe epilepsy. Medically refractory temporal lobe epilepsy has been shown to be associated with brain-wide reductions in regional cortical thickness or volume (Bernhardt et al., 2009; Lin et al., 2007; McDonald et al., 2008; Riederer et al., 2008; Bernhardt et al., 2010). A modest number of studies have identified brain changes beyond the primary lesion in focal cortical dysplasia, however reported extralesional changes in these studies are not typically atrophic (Bonilha et al., 2006; Colliot et al., 2006).

In this study, the difference between predicted and chronological age was cross-sectionally compared in three groups, comprising (i) individuals with medically refractory localization-related epilepsy being assessed for epilepsy surgery, (ii) newly diagnosed localization related epilepsy cases enrolled in the Human Epilepsy Project, and (iii) healthy matched controls imaged contemporaneously with epilepsy subjects. We used a previously validated multivariate machine-learning method for analysis of whole brain structural MRI to predict the age of individuals with focal epilepsy (Cole et al., 2015). This methodological framework allowed us to test the hypothesis that the brains of individuals with medically refractory epilepsy resemble those of older healthy individuals, as well as explicitly estimating the magnitude of the hypothesized aging effect. In addition to the primary analysis investigating increased neuroanatomical age in medically refractory cases, we also investigated whether age of seizure onset and

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Table 1
Demographic characteristics of study participants. Medically refractory epilepsy participants were recruited from the New York University Comprehensive Epilepsy Center presurgical assessment program. Newly diagnosed epilepsy participants were imaged as part of the Human Epilepsy Project.

Group	Number	Chronological age (years, mean ± SD)	Sex (M/F)
Medically refractory epilepsy	94	32.3 ± 13.6	48/46
Newly diagnosed epilepsy	42	31.4 ± 11.4	21/21
Healthy controls	74	28.9 ± 10.2	31/41

epilepsy duration were related to the difference between predicted and chronological neuroanatomical age.

2. Methods

2.1. Participants

Two epilepsy groups were included in the study. The first group comprised consecutively recruited individuals with medically refractory epilepsy referred for imaging as part of pre-surgical assessment at the NYU Comprehensive Epilepsy Center between 2007 and 2015. Investigations included clinical semiology, video-EEG monitoring, clinical MRI, neuropsychological assessment, and PET/SPECT when deemed appropriate by clinical investigators. Age of epilepsy onset was obtained from clinical records for these epilepsy patients.

The second group of epilepsy participants were recruited for the Human Epilepsy Project, an ongoing prospective study of newly diagnosed focal epilepsy. Participants were recruited if they were between 12 and 60 years of age and had a clinical history consistent with focal epilepsy and had two confirmed spontaneous seizures within the previous 12 months.

Healthy controls were recruited by community advertisement. Control participants were excluded if they reported prior history of psychiatric or neurological disorders, head injury or substance abuse.

For all participants whole brain T1 weighted MRI was obtained on a 3T Siemens Allegra scanner using an MPRAGE volumetric acquisition (voxel size 1.3 mm × 1 mm × 1.3 mm, echo time = 3.25 ms, repetition time = 2530 ms, inversion time = 1100 ms, flip angle = 7°).

2.2. Image analysis

The age of each individual was predicted using Pattern Recognition for Neuroimaging Toolbox (PRoNTo, http://www.mlnl.cs.ucl.ac.uk/pronto (Schrouff et al., 2013)). The prediction model was developed using T1-weighted MRI of healthy individuals obtained from 14 publicly available neuroimaging databases (total $N = 2001$, mean age = 36.95 ± 18.12 years, range 18–90, 1016 male, 985 female, see supplementary material for database list and demographic information (Adelstein et al., 2011; Beall and Lowe, 2007; Bron et al., 2015; Chao-Gan et al., 2010; Di Martino et al., 2014; Erickson et al., 2010; Gollub et al., 2013; Malone et al., 2013; Marcus et al., 2007; Mazziotta et al., 2001; Mennes et al., 2013; Nooner et al., 2012; Power et al., 2012; Tian et al., 2011)). Each T1 weighted MRI scan was segmented into gray matter and white matter and spatially warped into a common space to ensure voxelwise correspondence between individuals. The SPM software package was used for segmentation, non-linear (DARTEL) registration and resampling into Montreal Neurological Institute (MNI) 152 template space (Ashburner, 2007). Images were smoothed with a 4 mm FWHM kernel and modulated to ensure final images retained localized volumetric information from the original images. Each voxel in the final images thus represents a regional estimate of gray or white matter volume. A Gaussian processes regression (GPR) machine learning algorithm was then trained to predict chronological age using the gray matter and white matter maps (Rasmussen and Williams, 2005). The prediction accuracy of the GPR model was then assessed using k-fold cross-validation with $k = 10$, to generate predicted age values on all training images.

The accuracy of the model was quantified using the correlation between chronological age and predicted, the amount of variance in age explained by the model (R^2), the mean absolute error (MAE) and the root mean squared error (RMSE). The model was then applied to the GM and WM segments to provide an estimated age for all individuals in the study (medically refractory epilepsy, newly diagnosed epilepsy and the study-specific healthy control group).

The difference between the predicted age of the individual and their chronological age was calculated, where a positive value corresponded to an increased estimated neuroantomical age relative to chronological age. These values were then compared between the three groups using a general linear model, with age and sex included as covariates. We also investigated the effect of (i) age of onset and (ii) epilepsy duration on the difference between predicted and chronological age after controlling for age at the time of scan.

3. Results

Ninety-four individuals with refractory epilepsy, forty-two individuals with newly diagnosed epilepsy and seventy-four healthy controls were included in our study (Table 1). For the medically refractory epilepsy group, seizures were localized to the temporal lobe in forty-seven patients (50%), frontal lobe in eighteen patients (19%), parietal lobe in four patients (4%) and the occipital lobe in two patients (2%). The remaining twenty-three cases had adjacent multilobar seizure onset. Twelve of the forty-seven temporal lobe cases had histopathologically confirmed mesial temporal sclerosis, and twenty-two participants had focal cortical dysplasia. For the medically refractory group, seizure onset age ranged from one to fifty-three years of age (mean = 17.4; SD = 12.2 years) and epilepsy duration ranged from one to forty-five years (mean = 15.9; SD = 11.8 years). In the newly diagnosed epilepsy group, seizure onset age was between eleven and sixty (mean = 29.3, SD = 11.5 years) and epilepsy duration ranged from zero to nineteen years (mean = 2.1, SD = 3.9 years).

Cross-validation in the training dataset indicated that the model was able to accurately predict age ($r = 0.938$, $R^2 = 0.88$, MAE = 5.01, RMSE = 6.31), based on combined GM and WM volume images (permutation corrected $p = 0.001$). Accuracy estimates in the independent healthy control test dataset were: $r = 0.74$, $R^2 = 0.54$, MAE = 5.73, RMSE = 7.34.

Individuals with medically refractory epilepsy had a difference between predicted brain age and chronological age that was on average 4.5 years older than healthy controls (Fig. 1, $p = 4.6 \times 10^{-5}$). Although individuals with newly diagnosed epilepsy had a brain age 0.9 years older than their chronological age, this difference was not statistically significant ($p = 0.55$). There was a statistically significant relationship between age of onset and the difference in neuroanatomical and chronological age (−0.15 years difference per year, $p = 0.034$, $r = 0.5$). This finding indicates that the difference between predicted and chronological age is larger in individuals with earlier epilepsy onset. No significant relation-